June 15, 1999

MEMORANDUM

SUBJECT: Response to Public Comments on the Preliminary Risk Assessments for the Organophosphate Profenofos

FROM: Carmelita White, Chemical Review Manager
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Office of Pesticide Programs

TO: OPP Public Docket for Profenofos
Docket #34138

Introduction

This document addresses public comments that were received in response to EPA's Notice of Availability (63 FR 43175, August 12, 1998) of preliminary risk assessments for the first nine organophosphate chemicals: azinphos-methyl; bensulide; ethion; fenamiphos; isofenphos; naled; phorate; profenofos; and terbufos. (Note: All uses of isofenphos have been voluntarily canceled. (See 64 FR 28471, May 26, 1999.) Part I of this document addresses comments specific to profenofos and is divided into two sections: (A) comments from Novartis, the sole registrant and (B) comments from the general public. Part II focuses on non-chemical-specific comments. "Non-chemical-specific" means that the comment was submitted to the OPP Public Dockets for each of the nine chemicals or for a significant sub-set of the nine. Also, these non-chemical specific comments generally apply to regulatory or science policy issues that are not unique to any one of the risk assessments. The comments are presented in **bold** and the response is in normal typeset.

Part I: Profenofos Specific Comments and Responses

A. Response to Comments on the HED Chapter

Comment: **Novartis states that the rabbit dermal LD_{50} study (MRID# 42021501) which established a LD_{50} of 2560 mg/kg (males and females combined) is the appropriate study to use to establish the Toxicity Category. Novartis further noted that the dermal toxicity category based on this study should be revised from Toxicity Category I to Toxicity Category III (40 CFR, subpart 156.10). Table 2. of the HED chapter for the profenofos cites a dermal LD_{50} study in rabbits (MRID 00109427) which established a LD50 of 143 mg/kg for females (Toxicity Category I).**

Response**:** Both dermal LD_{50} studies (MRIDs 42021501 and 00109427), in addition to several other acute toxicity studies, were evaluated by the Agency. The study designated as MRID # 00109427 was determined to be the most appropriate acute dermal study for determining the toxicity category because it represented the most sensitive expression of dermal toxicity. Consistent with the results of that study, the Agency maintained the Toxicity Category I designation.

Comment: **Novartis states that, based on the results of the acute delayed neurotoxicity study in the hen using a refined formulation, the NOEL in the acute delayed neurotoxicity study was 117 mg/kg and the correct dose level for mortality was 234 mg/kg. The HED profenofos chapter, under the acute delayed neurotoxicity study in hen (MRID# 00126485) cites no delayed neurotoxicity, NOEL = 52 mg/kg (20 mg a.i./kg), 100 % mortality at next highest dose (104 mg/kg) and a LD_{50} = 127 mg/kg (56.3 mg a.i./kg)[b] as 52 mg/kg (20 mg a.i./kg).**

Response**:** The delayed neurotoxicity study in the hen is used to show potential delayed neurotoxicity. Since the study showed no delayed neurotoxicity, the numerical dose level has no effect on the risk assessment of profenofos. However, the Agency will examine the ambiguities in the dose levels associated with the delayed neurotoxicity study in hens and make any necessary corrections to the DER.

Comment: Novartis states that the acute neurotoxicity study in rats showed no histological neuropathy at any dose level and requested that the stated results at 190 mg/kg be revised. Multiple behavioral and clinical effects were observed at 190 mg/kg in the acute neurotoxicity study (MRID# 42939802) as stated in the RED chapter. These included an increased incidence of staining of the nose and compulsive licking (stereotypy), diarrhea, miosis, and abnormal gait. The LOEL for neurotoxicity was 190 mg/kg based on these multiple effects in each sex. The NOEL for neurotoxicity was 95 mg/kg.

Response: The Agency agrees that histological neuropathy was not reported, however, there were multiple behavioral and clinical signs of neurological effects at 190 mg/kg, which are considered to be adverse. The stated facts about the effects at 190 mg/kg will not be revised.

Comment: Novartis disagrees with NOELs for various endpoints (PP 12-13) in the HED RED chapter.

Response**:** The Agency believes the NOELs selected for profenofos are appropriate. The NOELs considered on the cited pages were carefully considered by the Agency's Hazard Identification Assessment Committee, who used scientific judgment and the weight of evidence in making the selections.

Comment: Novartis submits that the use of 800 A/day (for worker risk assessment purposes) is not representative of normal use patterns, since the possibility of a pilot treating

800 acres/day and using profenofos on all 800 acres in that day is extremely

remote. For aerial applications a more representative estimate of 350 A/day should be used to assess worker exposure.

Response: Consistent with past worker risk assessments for cotton, the Agency presented 800 A/day by aerial application as an "upper-end" estimate and 350 A/day by aerial application as a "typical" estimate. However, even when assuming 350 A/day are treated aerially, Margins of Exposure are less than 100 for mixer/loaders and applicators as indicated in the text of the chapter.

Comment: To refine the worker Margin of Exposure estimates Novartis is considering conducting a study to resolve the issue of the large difference between the NOEL (1 mg/kg/day) and the LOEL (10 mg/kg/day) determined in the 21-day dermal toxicity study. The end points used in quantifying the worker risk assessment were taken from this study. Novartis also states an intention to change the Curacron 8E packaging to a closed system for mixing/loading.

Response: The Agency commends Novartis for planning studies to narrow the NOEL and LOEL and acknowledges that there is a large difference between the NOEL of 1 mg/kg/day and the LOEL of 10 mg/kg/day. However, until the anticipated studies are submitted and evaluated, the endpoint/NOEL of 1 mg/kg/day will remain in place for Short-Term and Intermediate-Term Occupational risk assessment.

The Agency also commends Novartis for considering a change of packaging to a closed type system. However, it should be noted that this change in packaging will not alter the mixer/loader MOE estimate since the risk estimate already considered the use of engineering controls (closed system).

B. Response to Comments on the EFED Chapter

Comment: Novartis presented various arguments in response to the conclusion in the draft Ecological Chapter that use of profenofos on cotton presents high acute and chronic risks to nontarget birds and mammals. Novartis stated:

1) The risk quotient is based on an exposure value of 240 ppm, which is the maximum likely residue concentration on short grass immediately after application;
2) the amount of short grass in cotton fields is minimal;
3) the majority of birds associated with cotton are songbirds, but other species such as shorebirds and upland gamebirds are also present;
3) the diets of birds associated with cotton cultivation consists primarily of insects and seeds and not short grass;
4) most birds use habitats adjacent to but not in cotton fields; and
5) to the registrant's knowledge there have not been any field kill incidents involving

birds or mammals in the 15 years the chemical has been registered.

Response**:** The Agency recognizes that there are variables that must be considered in assessing risks. To this end, the Agency acknowledges that there is some validity in the registrant's points presented in items 2 through 5. However, the Agency must make assumptions when it lacks specific data to assess the potential risks and employs an accepted methodology. In this assessment, the primary influence on the risks to nontarget terrestrial organisms is the estimated environmental exposure concentration used to derive the risk quotients. The risk quotients derived from a comparison of estimated residues on avian and mammalian food items with LC_{50} are used as a risk index and are not absolute risk values. The values for both factors are chosen to compensate for uncertainty in exposure and hazard to nontarget wildlife.

When the Agency lacks sufficient data, the assessment will use assumptions that ensure protectiveness. The Agency used the Kenaga nomograph values, as modified by Fletcher et al (1994), because the values are based on a robust set of actual field residue data. According to Hoerger and Kenaga (1972), the upper limit values from the nomograph represent the 95^{th} percentile of residue values from actual field measurements. The modifications by Fletcher et al. (1994) are also based on measured field residues from 249 published research papers, including information on 118 species of plants, 121 pesticides, and 17 chemical classes. These modifications represent the 95^{th} percentile of the expanded data set. It is important to note that the Agency has encountered, during the chemical-specific registration process, wildlife food item residue data sets where measured residues equaled or exceeded those predicted by the nomograph.

In addition, pesticide regulatory decisions involve potentially widespread uses of pesticides, therefore, the Agency believes the use of upper limit values is necessary to account for the potential variability and uncertainty associated with application to a wide variety of use sites under a variety of environmental conditions. However, the Agency would consider reassessing the risks if chemical and use specific residue data became available, provided the data set is sufficiently robust to account for intra- and inter-site variability as well as account for temporally variable environmental conditions. Until such data are submitted, the Agency will continue to use the modified Kenaga nomograph values.

Comment: **Novartis disagrees that cotton fields are used extensively by birds**.

Response: To determine the extent of exposure, the Agency assesses the likelihood of species coming into contact with the chemical at its point of use or in the vicinity where the chemical may runoff. Based on field surveys, a large variety of birds are associated with cotton fields, including songbirds, upland gamebirds, gulls and terns. Waterfowl are also likely to be present in regions where cotton is irrigated.

For profenofos, two avian species were tested -- one waterfowl species and one upland gamebird species -- under the Fish and Wildlife Data Requirements listed in 40 CFR 158. To account for the

uncertainty that exists when extrapolating acute oral and subacute dietary data from two species to the large numbers of bird species associated with agricultural areas such as cotton, the Agency extrapolates this data to the most sensitive species expected to migrate in this area. The Agency's ecological database indicates that songbirds tend to be more sensitive than the two required test species, thereby, calculating risk with the maximum estimated environmental concentration helps compensate for this uncertainty in the toxicity data.

Comment: Novartis disagrees that birds and mammals use cotton fields and adjacent habitat for feeding, resting, and nesting.

Response: As stated previously, there is a misconception that wildlife in the adjacent edge habitat are not exposed to the pesticide at the levels present in the treated fields and consequently are not at risk. The edge habitat around the treated fields may receive the same amount of pesticide residues; the reduction in residue levels from spray applications often occurs some distance from the treated fields. Therefore wildlife in the edge habitat and those in the treated field are equally at risk.

Comment: Novartis indicated concern that there are no incident reports involving birds or mammals to raise a concern.

Response: The Agency does not believe that the lack of incident reports involving birds or mammals proves that animals are not dying from exposure to profenofos. Finding dead animals in the field is difficult, even when experienced field biologists are searching treated fields. Only carefully designed field studies can confidently indicate the likelihood of field kill incidents occurring. The Agency no longer requires field studies for organophosphate pesticides. However, based on the risk quotient mentioned above, the Agency concludes that use of profenofos on cotton presents high acute and chronic risk to birds and high acute risk to mammals.

Comment: Novartis disagrees that aquatic organisms are at high risk from spray drift and surface runoff.

Response: The Agency assessed available information and has concluded that there is a risk to nontarget aquatic organisms. Several fish-kill incidents were found in the Ecological Incident information System (EIIS) and the Agency received 6(a)(2) incident data from the registrant. This information was not cited in the original assessment, but has now been evaluated and has significantly affected our revised risk assessment. These incidents, reported in the Agency's Ecological Incident Information System (EIIS), include 13 fish kills attributed to profenofos between 1994 and 1996 (the only years currently listed in the database) in southern cotton-growing regions. In seven incidents, thousands of fish were killed per event, while more than 100 fish died in each of the other events. According to State reports the majority of the fish kills were attributable to surface water runoff and spray drift of profenofos based on tissue and water sample tests. The quality of the reported data is considered excellent and reliable.

The incidents indicate that, even when used according to label directions under normal agricultural practices, profenofos can reach fish-bearing waters in sufficient concentrations to result in large fish kills. Fish-kill incidents occurred since the product labels were last revised, indicating that existing label recommendations are inadequate to protect aquatic organisms. The aquatic risk is based on actual fish kill evidence rather than solely on modeling.

Comment: Novartis asked the Agency to reconsider its request for an additional full fish life cycle study (Guideline 72-5), based on their educational programs, buffer strips, existing chronic aquatic data, bridging studies from data with other acetylcholinesterase (AChE) inhibitors and existing data that indicates rapid degradation of the active ingredient.

Response: According to testing requirements contained in 40 CFR 158, a fish full life cycle study is required "when an end-use product is intended to be applied directly to water or is expected to be transported to water from the intended use site, when any of the following conditions are met: the EEC is equal to or greater than 0.1 of the NOEC in the fish early life stage study or the invertebrate life cycle study; or if studies of other organisms indicate that the reproductive physiology of fish may be affected." Also, the Agency requires studies on each active ingredient, not on classes of active ingredients. Data submitted on other AChE inhibitors cannot be used in determining the risks of profenofos to aquatic organisms. The presence of educational programs, buffer zones, or other mitigation actions are unrelated to the need for assessing the intrinsic hazard of a pesticide.

The Agency believes that it is still necessary to conduct a full fish life cycle study based on the above requirements and because the current EEC calculations are based on fate studies conducted under acid to neutral conditions. Since most of the fish kills reported tend to be located in regions with alkaline soils, the Agency believes that the fate studies may have been biased toward rapid degradation of profenofos and the reported EECs may underestimate the likely residue concentrations present in fish-bearing waters in the southern states. Water levels measured at the time the fish kills occurred ranged from less than 1 ppb to greater than 30 ppb, with most in the range of 0.6 to 1.5 ppb. These residue levels exceed 0.1 of the NOEC in the fish early life stage test. Therefore, they cannot be used as a criterion for determining the need of the fish life cycle study. In addition the criterion of reproductive impairment in other animals (birds and small mammals) is met. Therefore the fish life cycle study (72-5) for freshwater fish is needed to complete the chronic risk assessment of profenofos.

Comment: Novartis asked the Agency to reconsider its request for an estuarine fish early life stage study.

Response: The Agency requests an estuarine fish early life stage study, preferably on silverside, because of likely offsite transport of profenofos from cotton fields to estuarine waters and the high acute toxicity to estuarine fish. Depending on the results of this study, a fish full life cycle study on estuarine fish may also be required.

Comment: Novartis asked the Agency to reconsider its request for an estuarine invertebrate (mysid) life cycle study.

Response: The Agency will not require a new study. The Agency located in an internal database a scientifically valid mysid life cycle study submitted to the Agency in 1980, which fulfills the data requirement. The citation for this study is: " Hollister, T. 1980. Acute and Chronic Toxicity of Profenofos to Mysid Shrimp (*Mysidopsis bahia*), Project Number BP-80-2-40, EG&G Bionomics, Accession Number 246216." The results show the average number of offspring per hatch was significantly reduced in mysids exposed to $\geq$350 pptr; the NOEC was 220 pptr.

Comment: Novartis believes the Stewardship Program and precautionary label statements adequately eliminates the fish kill concerns and that no further testing is needed as verified through testimonials from the cotton growing states where the program is in place.

Response**:** The Agency requires scientifically valid field data, rather than testimonials, to verify that a program effectively eliminates fish kills. The Agency commends Novartis for instituting a stewardship program to educate users regarding application methods, recommending precautionary label revisions, and reporting positive results from the *Careful by Nature* program (memo from Novartis to the Agency dated August 28, 1998, D249641). The stewardship program is intended to "educate farmers, aerial applicators and consultants, emphasizing pesticide application methods to minimize fish kill events" by changing the practices of applying the pesticide just prior to rain and growing cotton to the edge of bodies of water. Claims that these programs have eliminated fish kills in Louisiana and decreased fish kills in Mississippi cannot be used in lieu of scientifically valid field data.

Part I.B. Comments from the General Public on the Draft EFED Chapter for Profenofos

Comment: The presence of enantiomers in organophosphate pesticides increases the overall toxicity of chemicals such as profenofos.

Response: Profenofos does not have a chiral center, and, therefore, cannot exist in isomeric forms that are enantiomeric (i.e., isomers whose mirror images are not superimposable). Therefore, the issue of specific enantiomers having greater toxicity than other enantiomers does not apply with profenofos.

Part II: Non-Chemical-Specific Comments and Responses

Non-chemical-specific comments were received from: American Crop Protection Association; Idaho Farm Bureau Federation; National Coalition Against the Misuse of Pesticides (NCAMP); National Cotton Council; Learning Disabilities Association; Fish and Wildlife Service, Division of Environmental Contaminants; Texas Agricultural Extension Service; Natural Resources Defense Council (NRDC); the Grocery Manufacturers of America, Michigan Agricultural Cooperative Marketing Association; U.S. Apple Association; Southern Professional Fruit Workers Conference (held at Clemson University); and 16 individuals, 13 of whom identified themselves as pest control operators (PCOs) or otherwise associated with the professional pest control industry.

Because there are several recurring issues in the comments that were submitted, we have chosen to divide our responses into two sub-sections. In order to avoid repetition, sub-section A deals with comments that are closely related and were repeated in more than one of the submissions, and with comments that are testimonial in nature. Sub-section B responds to those comments that are unique to each submission and refers the reader to the appropriate common responses in sub-section A.

A. EPA Responses to Recurring Issues in the Non-Chemical-Specific Comments

1. Comments Related to Common Mechanism of Toxicity

Comments: The Idaho Farm Bureau Federation felt that the criteria defining all organophosphate pesticides as having a common mechanism of toxicity are too broad, and that EPA should develop appropriate criteria for common mechanism. Other commentors, the NRDC and NCAMP, questioned why EPA has not considered a common mechanism of toxicity in these first nine OP risk assessments.

Response: With respect to developing criteria, EPA is required under FQPA to consider available information on the effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity. EPA believes that the organophosphate pesticides should be considered to operate via at least one common mechanism of toxicity--cholinesterase inhibition, unless and until the Agency receives data demonstrating otherwise.

In the Federal Register of August 6, 1998 (63 FR 42031 (FRL-5797-9), EPA issued a notice announcing the availability of the proposed EPA pesticide policy guidance document entitled "Guidance for Identifying Pesticide Chemicals That Have a Common Mechanism of Toxicity for Use in Assessing the Cumulative Toxic Effects of Pesticides." The guidance document describes the approach that EPA proposes to use for identifying and categorizing pesticide chemicals that have a common mechanism of toxicity for purposes of assessing the cumulative toxic effects of such pesticides. The 60-day comment period ended October 8, 1998. The revised guidance was issued in February, 1999. In developing this document, the Agency

solicited advice from the FIFRA Scientific Advisory Panel (SAP) in February 1997; a year later (March 1998), OPP reported its progress to the SAP.

With respect to the comments that EPA has not considered common mechanism in these first nine assessments, the Agency acknowledges that it has not yet performed a cumulative risk assessment, because the methodology for conducting such assessments is still being developed. Since there are currently no standard methods for doing cumulative risk assessment, EPA is pursuing an open, peer-reviewed process to develop approaches to cumulative risk assessment. The Agency is also nearing completion of the revision of the Chemical Mixtures Risk Assessment Guidelines, which present methods for combining risks from multiple chemicals. In addition, the International Life Sciences Institute (ILSI) is independently exploring appropriate methods and developing a framework for performing a cumulative risk assessment. ILSI held a workshop on this subject in September 1998, and will issue a report. The Agency will continue its ongoing efforts in this area along with examining the ILSI work and other sources of information in preparation for release of an Agency draft guidance document. This guidance document is currently scheduled for the late Summer or early Fall of 1999 with a 60-day comment period.

Until a method is available, EPA intends to complete risk assessments for individual OPs and proceed with the public process for development of risk mitigation strategies.

2. Comments Related to Additional Data, Data-Call-Ins, and Default Assumptions

Comments: The Idaho Farm Bureau Federation, thirteen individual comments from PCO's, and the National Cotton Council encouraged EPA to use its data call-in (DCI) authority to obtain the data necessary to conduct realistic risk assessments. The Cotton Council noted that comments in the Public Docket from the registrants indicated that, in some cases, data had been submitted, but have not been reviewed or considered in the preliminary risk assessments. A common theme was that EPA should use actual data, particularly usage data, and avoid default assumptions in its assessments.

Response: In phase four of reregistration, EPA exercised its data call-in authority to require studies to upgrade chemical data bases to current scientific standards. Most of the OPs were subject to reregistration DCIs and registrants have been allowed ample time to submit those studies. EPA makes its reregistration and tolerance reassessment decisions on the best data that are available. Where data are incomplete EPA may compensate by using an additional uncertainty factor or making a reasonable health-protective assumption. This has long been EPA practice, and is reinforced by FQPA's emphasis on the importance of the use of uncertainty factors where data are incomplete.

It should be noted, however, that the OP risk assessments in the docket are "preliminary," and that many of these first nine assessments were completed prior to receipt of all required data. During the public comment and response period, EPA has continued its evaluations of available

data, e.g., Monte Carlo analyses, for these first nine chemicals, and these evaluations have been incorporated into the revised risk assessments. In general, if additional, pertinent data are submitted prior to or during the comment periods, EPA will take these data into account in its final assessments and risk management options.

For a discussion of the sources of use and usage data and how EPA employs these data in its assessments, the reader is referred to a science policy paper entitled, "The Role of Use-Related Information in Pesticide Risk Assessment and Risk Management," which will be available shortly for public comment.

3. Comments Related to Inconsistencies in the Risk Assessments

Comments: NCAMP and others noted that the assessments for the nine OPs are inconsistent in format, level of refinement, assumptions used, and methods. For example, acute dietary risk is expressed in some assessments as a percentage of the reference dose (RfD), in others it is characterized by a margin of exposure. Drinking water risks are estimated in some assessments and not in others. It is not clear what risks are being aggregated and why.

Response: EPA acknowledges inconsistencies in the preliminary assessments for the first nine OPs. In many cases, the assessments were begun many months ago and have not been constantly updated to reflect new formats and methods. In the revised risk assessments we have made an effort to ensure consistency in the assumptions and the levels of refinement that are applied, given the data available for each chemical. For example, for drinking water, we have calculated acute and chronic DWLOCs for all chemicals and compared them to the levels estimated to be found in water. In the revised assessments, all acute dietary risks are now expressed as a percentage of the acute population adjusted dose (aPAD). (The aPAD is the reference dose including the FQPA safety factor. If the FQPA safety factor has been removed, the aRfD and the aPAD are the same.) We have attempted to identify major risk contributors (i.e., commodities or use patterns that contribute most to the risk), and have refined the residue estimates to the extent possible with existing data, including use of USDA Pesticide Data Program (PDP) and FDA monitoring data in some cases. In an attempt to make the risk assessments easier to understand and compare, EPA has prepared risk summary and overview documents for each OP. These risk overview documents have been prepared in a standard, logical format and are intended to assist the reader by identifying key features and findings of the risk assessments, as well as highlighting any assumptions and refinements that have been used.

4. Comments Related to Application of the FQPA 10X Safety Factor

Comments: The Learning Disabilities Association and the NRDC commented that EPA failed to demonstrate the existence of reliable data for most OPs to justify departure from the use of the FQPA 10X safety factor.

Response: OPP has developed criteria for retaining, reducing, and removing the ten-fold safety factor provided for in the FQPA to account for special susceptibility of infants and children to the effects of pesticide exposures. These criteria involve a weight-of-evidence consideration of both the nature and severity of effects observed in young animals, as well as the adequacy of the data base for the chemical. OPP's rationale for these criteria has been reviewed at various stages of development by the SAP. OPP has completed a draft Standard Operating Procedure (SOP) that provides procedural guidance at the working level for making recommendations for retaining or modifying the 10-fold factor.

In addition, an Intra-Agency workgroup is looking at general considerations regarding the FQPA safety factor decisions such as: establishing procedures for consistency and documentation; ensuring the adequacy of the data set for decision-making; and establishing criteria for retaining or modifying the FQPA factor.

The Agency's policy for applying the FQPA 10-fold safety factor is currently one of the science policy issues being prepared for public comment. Both the SOP and the Intra-Agency workgroup draft guidance document were discussed at the May, 1999 SAP meeting and are available for viewing on the OPP SAP web page: http://www.epa.gov/pesticides/SAP/. An FR Notice announcing the availability of these documents for public comment is expected shortly, with revised documents anticipated in the Fall.

The question of what constitutes a reliable data base for making decisions related to the FQPA safety factor is being thoroughly reviewed. Once that review process is completed, EPA may need to revisit its assessments and decide how best to incorporate the revised procedures into its ongoing decision making process.

5. Comments Related to Highly Exposed Populations

Comments: Both NCAMP and NRDC noted that EPA failed to consider the increased potential for pesticide exposure to "sentinel" populations, such as farm worker children.

Response: NRDC has petitioned the Agency to designate farm children as a major identifiable subgroup under the FQPA. The Agency is currently evaluating the scientific and legal issues raised in that petition. Specifically related to the preliminary risk assessments for the first nine OPs, EPA acknowledges that exposures to farm worker children were not evaluated separately, i.e., as a distinct population sub-group. However, based on the limited data currently available to characterize actual pesticide exposure to children of agricultural workers, such as a 1997 biomonitoring study by Loewenherz, Fenske and others (Environ. Health Perspect. 105:1344-1353), we believe that the exposure estimates developed by EPA using the Agency's Residential Exposure SOPs and other available information are reasonably inclusive of the exposures likely to be experienced by this sub-group.

EPA is concerned about the disproportionate exposure of farm children to pesticides and

has several ongoing projects designed to both assess and reduce these exposures. Some of EPA's major efforts in this area are described below.

EPA's major external research program, Science to Achieve Results (STAR) program allocated funds in fiscal year 1996 for three years of research on the most urgent issues regarding exposure of children to pesticides. The studies are looking at major types of exposure (touching, eating, crawling, etc.) and at seasonal and locational differences, including agricultural settings. This research will support regulations and public education efforts that are more fully protective of children, for example through revised use restrictions and labeling requirements, and improved training and public information materials. Under the STAR program, the University of Arizona is assessing exposure of the children of seasonal and migrant laborers to agricultural pesticides. In addition, the University of Washington is assessing, on a comprehensive seasonal basis, children's exposures to organophosphate pesticides.

EPA's National Center for Environmental Research and Quality Assurance of the Office of Research and Development is funding a grant with the University of California at Berkeley for a five-year study, that began in August 1998, to quantify the exposure of children in agricultural areas of California to pesticides. The project will integrate biological research with community-based intervention efforts. The study will determine the impacts of pesticide exposure on children's growth and development. The University will also work with the farm worker community to investigate approaches for reducing these exposures.

Finally, based on recommendations from the Children's Health Protection Advisory Committee (CHPAC), EPA has committed to conduct a national assessment of implementation and enforcement of the Worker Protection Standard, including its effectiveness in addressing the safety needs of women and children as agricultural workers.

6. Comments Related to the Role of OPs in Integrated Pest Management (IPM)

Comments: The Michigan Agricultural Cooperative Marketing Association, the Grocery Manufacturers of America and the Southeastern Professional Fruit Workers Conference noted that the loss of OPs would reduce the effectiveness of entire IPM programs. The loss of any tool in the IPM arsenal can result in greater overall use of pesticides and the return to prophylactic use of pesticides. IPM should be explicitly addressed in the risk assessment process.

Response: EPA recognizes the importance of some OPs in IPM and resistance management programs. We intend to consider these factors, as appropriate, in our risk management decisions. Specifically, under FQPA, EPA cannot use the biological or economic importance of a chemical as a factor in determining allowable dietary risk. However, if risk management is necessary, these factors would be considered in determining which chemical uses are most critical and should be retained.

7. Testimonial Comments

Comments: Two individuals provided comments that were testimonial in nature, that is, they expressed opinions but provided little or no specific information for the Agency to respond to. One person offered the view that OP's are "nerve gas" and all use should be banned. Another offered his support for the continued availability and use of phorate, terbufos, chlorpyrifos, methyl parathion, fonofos, carbaryl, carbofuran, and bromacil (only first 5 are OPs; only terbufos and phorate were among the first nine OPs.) The commentor noted that yields on his farm would be reduced without these products, but provided no documentation to quantify the yield loss.

Response: EPA recognizes the diversity of views exhibited by these comments.

B. EPA's Response to Submitter - Specific Comments

1. Comments from Private Citizens

Comment: One commentor urged EPA to account for "enantiomer" toxicity in reassessing tolerances for the OPs. Enantiomers are mirror image molecules produced in the manufacture of organophosphate active ingredients. Specifically, the commentor raises concern over the possibility that specific enantiomers of these substances could be produced during manufacture, and that these enantiomers may be more toxic than other enantiomers that may be present. Hence, the risks posed by these substances could be greater than the risks anticipated by EPA. The commentor would like to know specifically how EPA took into account the possibility of specific enantiomers and their toxicity during its risk assessment of the nine organophosphorus compounds and what procedures ensure that the current toxicity testing of active ingredients will reveal any potential problem with enantiomer contamination.

The commentor also referred to incidents "in Pakistan or Afghanistan and in the SW United States" related to the toxic effects of enantiomers of organophosphorus compounds in which "hundreds of people were killed."

The American Crop Protection Association (ACPA) submitted a comment to the docket which responded that normal toxicity testing for registration will test all of the enantiomers together. They also said that of the nine OPs only naled has a chiral center (a carbon atom bonded to four different groups), none of the others can possibly have enantiomers.

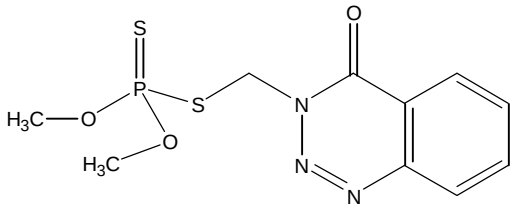
Response: Enantiomers of a given substance are isomers whose mirror images are not superimposable. While enantiomers of a given substance have identical physicochemical properties (except in the direction in which they rotate a plane of polarized light), they may vary in toxicity and, therefore, pose different risks to human health or the environment. In a given manufacturing process it is possible for more than one specific enantiomer of the product substance to form. It is also possible that one enantiomer may be produced more readily than another enantiomer, and may predominate in the commercial product. Even if an enantiomer is formed in low concentration

relative to another enantiomer during synthesis of a commercial product, it may still contribute significantly to the overall risk of the product if its toxicity is greater than the toxicity of the other enantiomer. EPA's Office of Pesticide Programs (OPP) routinely evaluates the manufacturing processes used to synthesize pesticides as part of its process to evaluate the risks posed by pesticides. The primary purpose of evaluating a manufacturing process of a given pesticide is to ascertain the composition of the technical product with regard to overall risk to human health and the environment. The evaluation includes an analysis and consideration of the feedstocks, reagents, catalysts, solvents and any other substances used in the process; reaction conditions; pesticide yield; byproducts, and any other substances that are known, or could reasonably be anticipated to form under the reaction conditions of the process. OPP also considers any impurities in the reactants or other substances used in the synthesis that may contaminate the technical product and contribute to overall risk.

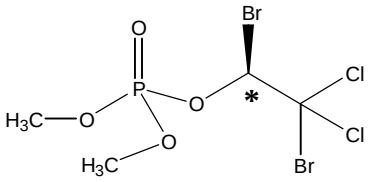
The structures of the nine organophosphorous substances are shown below. Naled has a chiral carbon atom (indicated with an asterisk), and fenamiphos, isofenphos and profenofos have chiral phosphorus atoms. Hence, two enantiomers are possible for naled, fenamiphos, isofenphos and profenofos. The other substances shown do not have chiral atoms and, therefore, it is not possible for them to exist as enantiomers. The Agency does not know the relative ratios of the specific enantiomers in the technical products of naled, fenamiphos, isofenphos and profenofos. However, the mammalian toxicity studies submitted by the registrants correspond to the technical products as manufactured, and reflect the actual toxicity of the technical products. The same is also true for the ecotoxicity studies submitted to the Agency. Therefore, even if one of the two enantiomers of any of the substances is substantially more toxic than the other enantiomer, and is present in the technical product, its toxicity would be expressed in the mammalian and ecotoxicity data submitted to the Agency and used in OPP's risk assessment of the technical product.

OPP also considers environmental fate during its risk assessment of a given pesticide. Environmental fate laboratory studies are typically conducted with a pure sample of the pesticide, radiolabelled at least at one site of the molecule. Separation of specific enantiomers of a pure sample prior to the environmental testing is not required, and usually not performed. The Agency recognizes, however, that a specific enantiomer of a substance could convert to another enantiomer under actual environmental conditions. Environmental photolysis, for example, may lead to interconversion of one enantiomer to another. OPP evaluates geometrical, configurational and/or conformational isomer interconversions, but only for those chemicals known to show specific isomer bioactivity. That is, one or more of the isomers are the only ones associated with pesticidal activity over the other isomers.

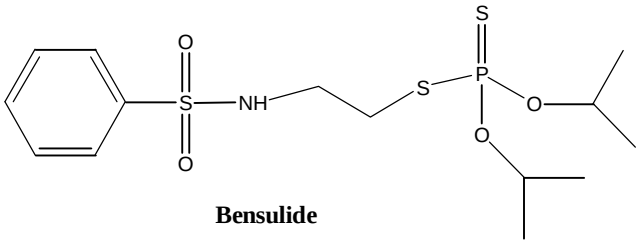
For naled, fenamiphos, isofenphos or profenofos, OPP does not have optical rotation data on any of the pure active ingredients to rule out or confirm the prevalence of one enantiomer over the other, or to conclude that the active ingredient exists as an equimolar (racemic) mixture. The environmental fate studies submitted for these substances were not intended to follow the fate of individual enantiomers in regard to enantiomeric interconversions. Hence, OPP does not know to what extent, if at all, the individual enantiomers of naled, fenamiphos, isofenphos or profenofos



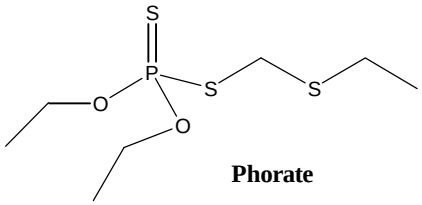
Azinphos-methyl



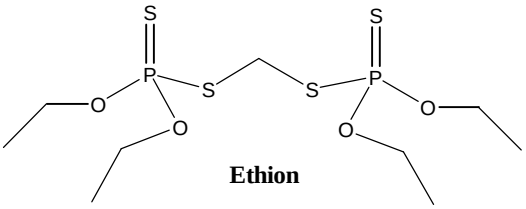
Naled



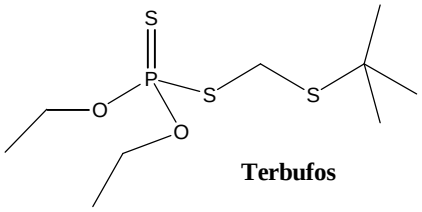
Bensulide



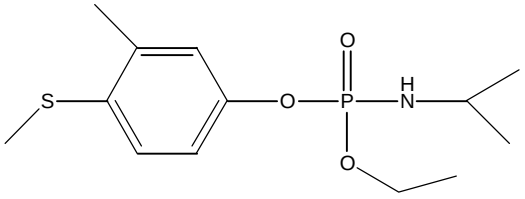
Phorate



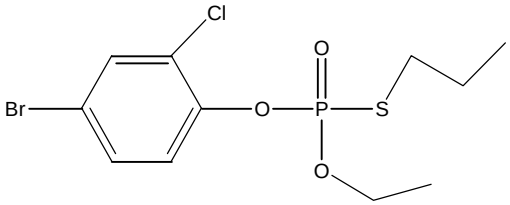
Ethion



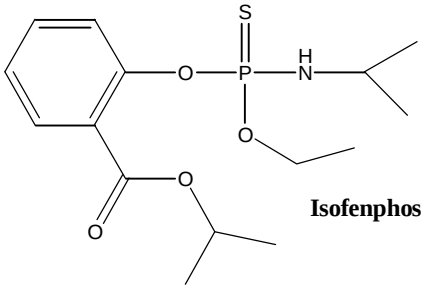
Terbufos



Fenamiphos



Profenophos



Isofenphos

interconvert in the environment. In addition, data are lacking regarding the mammalian toxicity and ecotoxicity of the individual enantiomers of these substances. Because of these data gaps, there is no basis from which OPP can consider in its risk assessments of these substances the possibility of, and extent to which the specific enantiomers of these substances may interconvert in the environment and the impact that such interconversions may have on human health and the environment.

It should be noted that EPA has recently published a Federal Register notice requesting public comment on how the Agency should handle registration of pesticide active ingredients (AIs) that are composed of chemical isomers. Among other issues, the notice solicits comment on whether or not an AI originally registered at a particular proportion of isomers should be subsequently registered as a new AI when purified for one or more chemically active isomers. The notice was published in the Federal Register on April 28, 1999, Volume 64, Number 81, Pages 22863-22865. Comments, identified by the docket control number "OPP-00580", must be received by June 28, 1999. EPA will consider comments received in developing a policy on registration of isomeric active ingredients.

As to the commentor's reference to large numbers of deaths resulting from OPs, EPA has no record of pesticide poisoning incidents of the magnitude described. One incident was reported in Pakistan among malaria workers. In this instance there was an abrupt shift from DDT to malathion use for mosquito control. One of the malathion batches was contaminated with the more toxic isomalathion, resulting in numerous exposures and possibly five deaths.

Anyone with specific knowledge of harmful incidents related to OP use or OP contamination with enantiomers is encouraged to submit them to EPA, so they can be considered in our risk assessments. Incident information is most useful if it contains sufficient detail to determine the circumstances of exposures, e.g., was it an accident or misuse, what symptoms were observed, how severe and long lasting were the symptoms, etc.

2. Comments from Growers, Commodity and Marketing Groups

Comment: The Idaho Farm Bureau Federation felt that the criteria defining all OPs as having a common mechanism of toxicity are too broad. EPA should take time to develop appropriate criteria for common mechanism, gather actual data rather than rely on conservative default assumptions, and communicate decisions to all stakeholders. The Federation supports Vice President Gore's directive to have an open and transparent process, a reasonable transition to alternative products, and the use of sound science. They believe that sound science dictates not allowing decisions to be driven by a statutory time frame. The Federation offers assistance with usage questions.

Response: EPA is committed to the principles outlined by Vice President Gore. It is primarily for that reason that the Tolerance Reassessment Advisory Committee (TRAC) was formed and the pilot process for increased public participation in pesticide decisions was developed. However,

EPA must balance the goal of providing for greater transparency and participation in development of science policy with its mission to ensure the safety of the food supply and the health of consumers--especially children, workers, and the environment. In order to accomplish our mission through timely decision making, EPA has established an ambitious schedule for completion of individual OP risk assessments and development of risk management options. It should also be noted that FQPA does establish a statutory deadline to complete the reassessment of existing tolerances by 2006, and the Agency is making every effort to comply with that deadline.

See also responses to II.A.1 and II.A.2 above.

Comment: The National Cotton Council notes that registrant comments in the dockets indicate relevant data were not considered in the assessments. Publishing risk assessments that are incomplete and thus inaccurate does not enhance the process, exemplify sound science, or inspire confidence in the growers that EPA will make good decisions. The Council is concerned that exposures from gin trash as a feed additive are grossly overestimated. No cotton uses should be canceled based solely on unacceptable risk resulting from gin byproducts using current EPA assumptions. (Note: OPs with cotton uses include azinphos-methyl, phorate, profenofos, naled, dicrotophos, and DEF (tribufos). The Council is working with the Agency to "adjust" these assumptions.

Response: EPA representatives recently (10/13/98) met with a delegation from National Cotton Council (NCC) in response to their request to discuss cotton gin byproducts (CGB) and its proportion in livestock feeds. In addition to members of the NCC, representatives of cotton ginners associations (Texas Cotton Ginners Association, Southeastern Cotton Ginners

Association, and the California Cotton Ginners Association) were present. These experts are familiar with CGB, its volume of production in the USA, and its use as animal feed.

EPA discussed how a risk assessment is performed, i.e., how CGB are factored into the beef and dairy cattle diets and how potential transfer of residues to meat and milk could therefore affect a person's daily dietary intake of pesticide residues. Table 1 of OPPTS Test Guidelines Series 860 currently lists CGB as a raw agricultural commodity as comprising up to 20% of the diet of beef and dairy cattle.

Representatives of the ginners associations agreed that in some parts of the country CGB are fed at up to 10% of the diet to beef cattle when the cattle first enter the feed lot. CGB are then reduced to approximately 3% in the finishing rations. Based on this information, the NCC has asked EPA to reconsider how CGB are currently listed in Table 1.

EPA asked the NCC to provide detailed information concerning the disposition and use of CGB. Information submitted should be able to be independently verified by OPP. The NCC agreed to submit a protocol for obtaining such information.

See also response to II.A.2 above.

Comment: The Michigan Agricultural Cooperative Marketing Association notes that phorate fits well into growers established IPM plans to minimize pest resistance. Its loss would reduce effectiveness of the entire IPM program. Azinphos-methyl is essential to blueberries and tart cherries-- Michigan is a leading producer of these commodities in the US. No quantitative loss estimates were are given. The Association encourages EPA or USDA to obtain from growers on a national level the necessary use data which will satisfy the crop-pest-pesticide requirements so that proper FQPA decisions can be made.

The Association notes that the Michigan Department of Agriculture is completing a research project designed to evaluate the impacts of various production and handling practices on pesticide residues on food. The project was funded by EPA Region 5 and will test samples at the farm gate and at various stages during processing to quantify residue reductions. The Association urges EPA not to make any determinations--interim or final--until science policy issues are resolved; they acknowledge the magnitude of the task facing EPA in implementing FQPA and offer assistance.

Response: EPA has contacted Michigan State University to determine the scope and timing of the research that was described in this comment. The project is currently focusing on apples, peaches, blueberries, cucumbers, squash and potatoes, but other commodities are planned. The analysis of field data is scheduled for completion in 1999. Until these data are submitted and reviewed, we cannot comment on how they will impact current assessments. However, EPA notes that this type of data, i.e., linking actual application rates and practices with residue reduction from various processing techniques, could be very useful in determining pesticide-crop specific processing factors for refining residue estimates. If these data are received in a timely manner, they can be considered in EPA's ongoing assessments.

See also response II.A.6 above.

Comment: US Apple Association has worked with the Agency to develop data that could refine residue estimates and has submitted such data to the Agency. However, it is impossible to ascertain from the preliminary risk assessment in the docket, what data were used in the azinphos-methyl apple assessment.

Response: This comment primarily relates to azinphos-methyl; however, a general discussion of how EPA employs use and usage data may be helpful. EPA has various sources for these data including USDA, California EPA, National Center for Food and Agriculture Policy, grower groups, as well as proprietary sources. These data tend to be more robust for major crops such as corn and cotton, and less so for minor crops. It is for these minor crops that usage data from growers can be most useful. In general, EPA incorporates use and usage data in a number of ways to assess dietary risk. Initial refinement involves incorporating the percentage of the crop that is actually treated (%CT). Further refinements involve applying processing factors, and calculating

residue decline and residue degradation where data are available to quantify these residue reductions. Additionally, an apple cooking study on baby food could reduce the estimated dietary risk. Also, single serving data on apples could reduce or increase the estimated dietary risk.

Growers and others frequently point out that the actual or typical application rates and frequencies are lower than labeled rates and that actual PHIs are longer than those specified on the product labels, and that these typical values should be used in EPA's risk assessments. This information is useful to the Agency only if it is accompanied by data to quantify residue reductions from longer PHIs, lower application rates, etc. Further, in order for the Agency to be able to rely on lower application rates and longer PHIs in its risk management decisions, product labels may need to be revised to reflect these refinements.

In its refined risk assessments, EPA has tried to show clearly which refinements have been applied to each crop. For example, for azinphos-methyl the revised risk assessment has an appendix table of crop by crop descriptions of specific data used in the revised analysis. This table clearly indicates that the Agency used USDA Pesticide Data Program (PDP) and FDA monitoring data for 80% of foods treated.

Comment: The Grocery Manufacturers of America emphasized four general points: 1) the importance of sound scientific principles; 2) the importance of using all available data to the maximum extent feasible; 3) ensuring the availability of chemicals required for IPM programs; and 4) validate all models and methods before use for regulatory purposes.

EPA should use both monitoring data and processing studies wherever possible, including PDP, and FDA data and actual use practices rather than theoretical maximums and assumptions.

Response: Until now, EPA has used PDP monitoring data in acute dietary assessments only for blended commodities, such as apple sauce and tomato paste. EPA has not used PDP data for single serving commodities, such a single fresh apple or a baked potato, because PDP data are derived from composite samples, and do not represent the highest concentrations that could be found in individual single servings. It is these potentially high residues that are of concern for acute dietary risk assessments. However, recently EPA has developed a statistical method to determine the range of residue values comprising composited samples for certain commodities. This method has been applied to several of the acute dietary assessments for the first 9 OPs, including azinphos-methyl. It is currently undergoing additional peer review.

See also responses to II.A.2, II.A.3, and II.A.6 above.

3. Comments from Environmental and Consumer Groups

Comment: The National Coalition Against the Misuse of Pesticides (NCAMP) questions why EPA has made only nine assessments available to the public and why the Agency has ignored common mechanism. NCAMP compared methodology across all nine assessments and found

inconsistencies in methods, different ways of combining risks, different assumptions, data sources used, and formats.

For example, in the Human Health Assessments NCAMP feels that real world exposures such as drift, routine misuse, exposure to multiple chemicals, and exposures to children of farm workers were ignored. Similarly, for Ecological Risk Assessments, multiple routes of exposure should be considered, e.g. direct application, runoff, drift, bioaccumulation, etc. Direct and indirect (food chain) effects should also be considered.

For all assessments, not all inerts, contaminants, metabolites and degradation products were considered. EPA ignored sources such as NCAMP, other non-profits and Agencies, and open literature for incident and other information. EPA's assessments fail the criteria of transparency; EPA should produce a guide to all OP risk assessments summarizing hazard, exposures and why risks have not been combined.

Response: EPA considers, on a routine basis, a number of the factors that NCAMP lists as omissions in our risk assessments. Some of these considerations are standard procedures and as such, are not mentioned in every risk assessment. For example, both technical active ingredients and end-use products are tested for comparative toxicity and composition. If inerts, contaminants, degradates or metabolites of toxicological concern are identified, we can require additional data, both toxicity and environmental fate data, if necessary, on those substances. EPA's Inert Ingredients Policy identified inerts of most concern, required testing and labeling for certain classes of inerts, and has resulted in a shift from more to less toxic inerts in pesticide products.

When studies are brought to the Agency’s attention, EPA can and has used information from the open literature for its risk assessments. For example, EPA's "Hazard Assessment of the Organophosphates" (July 1998) mentions literature studies as part of the weight-of-evidence considerations for acephate, chlorpyrifos, malathion, and methamidophos.

EPA routinely considers incident information in its risk assessments. The Agency maintains data bases of incidents related to human poisoning from pesticides, contamination of water resources, and wildlife exposures and die-offs due to pesticide exposure. We work with states, particularly California, other government agencies, and private organizations, such as Poison Control Centers to obtain accurate and up-to-date information related to pesticide exposure incidents of all kinds. We encourage NCAMP, through this public comment process, to actually provide EPA with any information that they may have relevant to the risk assessment of the OPs, rather than simply noting the existence of such information.

See also responses to II.A.3. and II.A.5 above.

Comment: The Learning Disabilities Association (LDA) notes that none of the first nine organophosphate chemical risk assessments retained the FQPA 10X factor. In the Report of the FQPA Safety Factor Committee, EPA found no evidence of enhanced susceptibility for 33 of 40

OPs. LDA seriously questions this conclusion based on two factors. First, is the inadequacy of the developmental neurotoxicity database. This is the only study that looks at functional effects like learning and memory. If EPA does not have developmental neurotoxicity data, how can we be sure there are no functional effects. Second is EPA's tendency to disregard offspring toxicity as "secondary" to maternal toxicity. LDA believes that even if developmental effects occur at higher doses than maternal, the maternal effects could be transient, and the effects in offspring might be permanent.

LDA requests EPA to defer final decisions on the FQPA 10X safety factor for all OPs until the expert panel recommendations for what constitutes an appropriate toxicity and exposure data base for making 10X determinations are available in late December.

Response: EPA's process for reviewing current procedures related to the 10-fold FQPA safety factor are described in detail above in section II.A.4. The Agency is currently beginning the public participation process to develop risk mitigation for the first nine OPs. Developing and implementing interim mitigation for these chemicals now does not preclude additional mitigation and/or data requirements in the future in response to new or revised policies and guidance. With few exceptions, the Agency's decisions related to the OPs cannot be considered final until a cumulative assessment has been conducted.
See also response to II.A.4 above.

Comment: The Natural Resources Defense Council (NRDC) submitted a copy of their report, "Putting Children First," and provided comments on four broad issues: 1) EPA fails to demonstrate the existence of reliable data for most OPs to justify departure from the use of FQPA 10X safety factor; 2) preliminary assessments do not provide reasonable certainty of no harm, e.g. EPA did not consider "sentinel" population of farmworker children; 3) EPA must conduct a cumulative assessment; and 4) often, e.g., for azinphos-methyl, occupational risks are unacceptable even with maximum mitigation. These should be eliminated expeditiously.

Response: EPA intends to complete risk assessments for individual OPs, taking into account any comments received during the public comment period. For the first nine OPs, the public comment period closed on the preliminary risk assessments in October, 1998. According to the plan developed by the TRAC, EPA will revise the risk assessments, respond to comments on the preliminary risk assessments, hold a Technical Briefing, and work with USDA and stakeholders to solicit risk management ideas.

See also responses to II.A.1, II.A.4, and II.A.5 above.

4. Comments from Other Federal Agencies

Comment: The Fish and Wildlife Service, Division of Environmental Contaminants, pointed out that all nine of the OPs have Final Biological Opinions (1989) for Endangered Species. FWS recommends that EPA implement, at a minimum, via label modifications and county bulletins, the

applicable Reasonable and Prudent Alternative measures identified in 1989 Biological Opinions. EPA should also implement the risk reduction and mitigative measures identified in the OP ecological risk assessment documents to reduce hazards to non-target organisms.

Response: EPA is in the process of developing county-specific bulletins that specify measures to protect endangered and threatened species. Although bulletins have not yet been developed for all counties where they will be needed, EPA has included the pesticide use provisions from the 1989 Biological Opinion (as well as other opinions) or equivalent protective measures in the over 300 bulletins that have been completed and distributed.

The mitigation measures suggested in the preliminary ecological risk assessments, along with other measures that may be put forward during the comment period, will be considered in developing risk management strategies for these nine OPs.

5. Comments from Universities and Extension Services

Comment: The Texas Agricultural Extension Service provided a preliminary economic assessment of the withdrawal of certain FQPA target pesticides on prominent vegetable crops (onions, melons, carrots, crucifers and peppers) in the Rio Grande Valley of Texas. The report examines changes in yield and estimated economic losses in farm revenue, from the loss of various chemicals and combinations of chemicals including the OPs, bensulide, diazinon, dimethoate, disulfoton, chlorpyrifos. The assessment includes several other non-OP pesticides.

Response: This information has been provided to our Biological and Economic Analysis Division and to the Chemical Review Managers for the listed chemicals for use in developing risk mitigation options. Under the provisions of FQPA, EPA can not use benefits information as a rationale for exceeding acceptable dietary risk levels. However, such information could be useful in considering risks and developing transition strategies, if such strategies become necessary.

Comment: The Southeastern Professional Fruit Workers Conference, the annual meeting of applied fruit scientists (held at Clemson University in October, 1998) provided their evaluation of the OPs (and other pesticides) that are crucial in resistance management and IPM programs for crops in their area.. The group identifies opportunities for mitigation (primarily reductions in numbers of applications and increased PHIs). *(Note: This comment was submitted after the dockets for the first nine OPs closed. However, because it pertains to some of the first nine, we have chosen to address it in the first response document.)*

Response: This information has been provided to our Biological and Economic Analysis Division and to each of the Chemical Review Managers for the chemicals named in the analysis. This type of information is useful to the Agency in determining the feasibility of mitigation such as reduced frequency and timing of pesticide applications, and in considering risk trade-offs, where appropriate.